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The use of granulocyte colony stimulating factor to enhance oocyte release in women with the luteinized unruptured follicle syndrome

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Summary

Purpose: To determine if an injection of granulocyte colony stimulating factor (G-CSF) prevoulatory can enable oocyte release from the follicle in women who have failed to release in natural cycles despite an endogenous luteinizing hormone (LH) surge, and also despite treatment with human chorionic gonadotropin (hCG) or a gonadotropin releasing hormone agonist (GnRHa). *Materials and Methods:* A single injection of 100 mg G-CSF was given in the late follicular phase followed by hCG 10,000 units at peak follicular maturation in women with at least three consecutive cycles of luteinization without oocyte release. *Results:* Six women had ten cycles with G-CSF and hCG. Definite release occurred in four, inconclusive in four, and definitely the luteinized unruptured follicle in two. Biochemical pregnancies occurred in two of the cycles where oocyte release occurred and a live delivered pregnancy in another cycle of release. *Conclusions:* Without controls one cannot state with certainty that G-CSF enabled oocyte release when hCG and leuprolide failed. Nevertheless, the data do support a trial with G-CSF before proceeding to IVF-ET.

Key words: Luteinized unruptured follicle syndrome; Granulocyte colony stimulating factor; Human chorionic gonadotropin; Gonadotropin releasing hormone agonists; Natural cycles.

Introduction

Though there is not universal agreement that pelvic sonography can determine with a reasonable certainty oocyte release, it appears that some women have a tendency to not release the oocyte from the follicle despite luteinization [1, 2].

There are data suggesting that though human chorionic gonadotropin (hCG) injection may help to release oocytes in some women who have the trend for non-release (termed the luteinized unruptured follicle syndrome or LUF) a 10,000 IU injection of hCG does not always correct the defect [3]. In some circumstances raising endogenous LH and/or FSH levels by the use of a gonadotropin releasing hormone agonist, e.g., leuprolide acetate, can enable oocyte release even when hCG has failed [4, 5].

Granulocyte-colony stimulating factor (G-CSF) is an inflammatory cytokine present mainly in granulosa cells [6]. There is evidence that mRNA for G-CSF was ten times higher in the late follicular phase than in other phases [7].

Indeed Espy proposed a hypothesis that ovulation is an inflammatory process [8]. Besides G-CSF, other inflammatory cytokines, e.g., interleukin (IL)-1, IL-6, tumor necrosis factor alpha, granulocyte macrophage colony stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF) have shown increased levels in the pre-ovulatory follicle [9-14].

Because some studies have found that compared to other inflammatory cytokines, e.g., IL-1B and IL-6, only G-CSF showed a significant increase in the serum during the ovulation phase [15], it was decided to see if oocyte release could be achieved in women with LUF syndrome who previously failed to release with hCG and GnRH agonists.

Materials and Methods

Women failing to demonstrate collapse of the follicle (shrinkage by > five mm) before the serum P exceeded two ng/ml first in a completely natural cycle, then a natural cycle where 10,000 units of hCG was given at the time of peak follicular maturation, and a third failure despite three s.c injections of one-mg leuprolide acetate given 12 hours apart also at the time of peak follicular maturation were enlisted.

G-CSF 100 mg s.c. was given as soon as the serum E2 approached 200 pg/ml (usually two days before hCG 10,000 unit injection). Failure of the follicle to shrink at all before the serum P exceeded two ng/ml was considered LUF. Shrinkage by only three to four mm was considered borderline release. Pregnancy rates were compared in those who appeared to release oocytes *vs.* those with inconclusive release vs. those with definite LUF. A pregnancy that did not proceed to ultrasound evidence of pregnancy but showed at lease one rising level of serum beta hCG, was counted as pregnancy achievement.

Only women with patent fallopian tubes and male partners with normal semen parameters were selected.

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Results

Six women were enlisted with long-term infertility who fulfilled the aforementioned criteria for selection. G-CSF (filgrastim was given in ten natural cycles. Oocyte release occurred in four of ten cycles (40%). Conclusive LUF was found in only two cycles (20%). Inconclusive release occurred in four cycles. One woman failed to release in both cycles. One woman failed to release in the first cycle but released in second cycle. Thus LUF only occurred in one of six (16.69%) women.

Three of six women released an oocyte (one woman in both cycles and one woman in one of two cycles) and two of them had biochemical pregnancies and one 43-year-old woman (G-0) delivered a live baby. None of the two women with inconclusive release conceived.

Discussion

Infertile women despite regular menses and attaining adequate mid-luteal phase serum progesterone levels may still have subtle ovulatory defects [16]. These defects include releasing the oocyte before the follicle is mature [17], premature luteinization [18], a short follicular phase [19], or merely the insufficient production of progesterone by the corpus luteum [20,21].

As mentioned, the luteinized unruptured follicle syndrome may be another subtle ovulatory defect, which when corrected, leads to pregnancies [1-5]. Though not uncommon as an isolated phenomenon (as in frequently the etiologic factor for the development of ovarian cysts), the occurrence of non-release of the oocytes in the majority of natural cycles (and thus considered the LUF syndrome) is relatively uncommon [1]. Even less common are women with LUF syndrome who fail to release oocytes even with hCG or GnRH agonists [3, 5]. Thus, it would be extremely difficult to perform a randomized prospective placebo controlled study from one institution to evaluate the efficacy of G-CSF in correcting the LUF syndrome in oocyte release failures even with hCG or GnRH agonist treatment. Similarly, there is probably insufficient interest to establish a multicenter study to acquire more statistical power.

This small series does not clearly prove that G-CSF was needed to enable oocyte release as compared to a fortuitous chance. Nevertheless, it is worth trying a new therapy, e.g., G-CSF, when everything else has failed rather than the very expensive option of mechanically removing the eggs from the follicle, i.e., in vitro fertilization.

A search of the literature was not able to find the use of G-CSF for LUF in natural cycles. However, the authors did find one study of a comparison of 16 women treated with clomiphene citrate and hCG [15]. Whereas only 56.5% showed oocyte release in the clomiphene hCG cycles, the addition of G-CSF (in this case filgrastim) resulted in a release rate of 88.9% [15]. Their definition of release included follicle collapse even five days after hCG without regards to the serum P level, so they may have assumed some women released when by the present authors' definition they would not have released [15].

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